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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/993,045	11/13/2001	Timothy R. Brazelton	286002021300	8147

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EXAMINER	
LI, QIAN JANICE	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 11/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/993,045	BRAZELTON ET AL.	
	Examiner	Art Unit	
	Q. Janice Li, M.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-13,15-17,21 and 36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-13,15-17,21 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The response and amendment filed September 11, 2006 are acknowledged. Claims 2, 3, 14, 18-20, 22-35 have been canceled. Claim 36 is newly submitted. Claims 1, 4-13, 15-17, 21, 36 are under current examination.

Claim Rejection

Claims 1, 4-13, 15-17, 21, 36 are objected to because of the claim recitation "administering...bone marrow-**derived** cells". In light of the specification, these cells are bone marrow cells, not any other cell *derived* from bone marrow cells. Hence, it would be more clear and appropriate to use the term "bone marrow cells" in place of "bone marrow-derived cells", since the administered cells do not undergo any derivation process before administered intravenously.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-13, 15-17, 21, 36 stand or newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for delivering syngenic or allogenic marrow cells to the brain of a subject via intravenous administration of unfractionated (whole) bone marrow cells, does not reasonably provide enablement for

treating a neuronal deficiency caused by Parkinson's disease with BM-derived (any fraction of) cells, or autologous bone marrow cells to a recipient, and by any vascular route of delivery. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

In the remarks, the applicant first cited *In re Brana* and argue that they predicted that bone marrow-derived neuronal cells can compensate for the loss of functioning neuronal cells in diseases such as Parkinson's, and performing the method and achieving the outcome as claimed require no undue experimentation.

In response, the prediction has yet to be proven true. It is noted performing bone marrow transplantation may be routine, achieving the outcome as claimed, i.e. treating neuronal deficiency caused by Parkinson's disease, has far from reality years after instant priority date as evidenced by the cited references of record. It is noted the Office does not request safety and efficacy data, but basic enablement requirement for the claimed invention, i.e. treating neuron deficiency of Parkinson's disease, this is the responsibility of the PTO.

Concerning the applicant's observation in a mouse MPTP model, the applicant cited several publications showing the relevance of the MPTP-toxin PD model and Parkinson's disease in humans.

In response, indeed, this model is an art-acknowledged model for investigation of PD, and has been important in our understanding of PD and in the development of *symptomatic* treatments of PD. However, since the MPTP-toxin PD model does not fully

correlates with the human Parkinson's disease in many different levels as taught by *Fleming et al* (NeuroRx 2005;2:495-503), symptomatic improvement in the mouse model does not equal to the success of treating neuron deficiency of PD in humans, because the symptomatic improvement in the mouse model may not be translated to the same effect in PD patients since the cause for the symptom is still under investigation, and can't be the same between the animal model and the human PD, and is not the same in the mouse model vs. in PD patients. Taken the *Eslamboli* review newly cited by the applicant, *Eslamboli* (Brain Res Bull 2005;68:140-9, abstract cited by the applicant) teach, "THERE ARE SUBTLE BUT SIGNIFICANT DIFFERENTCES BETWEEN RODENTS AND MONKEYS/HUMANS IN THE ANATOMICAL STRUCTURES INVOLVED IN THE PATHOLOGY OF PD" (§ 2, page 141). *German et al* (Neurodegeneration 1996;5:299-312, abstract cited by the applicant) while acknowledge that administration of high doses of MPTP to certain mouse species produces a pattern of midbrain DA cell loss that resembles that observed in patients with idiopathic PD, also teach, "STRIATAL DOPAMINE DEPLETION IS NOT NECESSARILY EQUIVALENT TO MIDBRAIN DA CELL DEGENERATION" (column 2, page 310). This is true particularly considering what was known in the art at the time of instant priority date, and current state of the art years after instant filing as illustrated by *Hows* (Trans Immunol 2005;14:221-3), who was fully aware of applicant's discovery five years earlier, reviewed many remain questions in the art with respect to treating PD with adult bone marrow stem cells, and cautioned "THERE HAS BEEN A RECENT SURGE OF INTEREST IN THE THERAPEUTIC **POTENTIAL** OF ADULT HUMAN STEM CELLS. MUCH OF THE PUBLISHED WORK IS **CONTRADICTORY** EMPHASIZING THE NEED FOR CONTINUED HIGH QUALITY RESEARCH ON THE MOLECULAR AND CELLULAR PROCESSES INVOLVED BEFORE PROCEEDING TO ATTEMPTING THE

CLINICAL APPLICATION OF ADULT MARROW STEM CELL THERAPY FOR DEGENERATIVE DISEASE AND TO REPAIR TISSUE DAMAGE ON A LARGE SCALE" (last paragraph, page 223, emphasis added). *Sigurjonsson et al* (PNAS 205;102:5227-32, IDS) point to insufficient rate of neuronal differentiation *in vivo*, which is insufficient for providing any therapeutic effect for any disease, "ADULT HSCS FROM RODENTS AND HUMANS INJECTED INTRAVENOUSLY OR INTRACEREBRALLY INTO RODENT HOSTS CAN SETTLE IN THE BRAIN AND EXPRESS NEURONAL MARKERS, BUT THE INCIDENCE OF NEURONAL DIFFERENTIATION HAS NEVER BEEN REPORTED TO EXCEED 1-2% OF THOSE HSCS THAT INTEGRATE INTO THE BRAIN" (column 2, page 5227, emphasis added). Clearly, at such a low rate of neuronal differentiation, and uncertainty of neuron phenotype and function *in vivo*, any therapeutic effect of mobilized BMDCs on treating a neuronal deficiency would be remote. In a post-filing publication, instant inventor concurs (*Pomerantz & Blau*, Nat Cell Biol 2004;6:810-6, IDS), "MAJOR CHALLENGES EXIST IN THE USE OF BMDCS IN A CELL-BASED THERAPY FOR NON-HEMATOPOIETIC TISSUES, INCLUDING INCREASING THEIR EFFICIENCY OF INCORPORTION INTO TARGET TISSUES AND DEMONSTRATING EFFICACY IN TREATING TISSUE MALFUNCTION" (column 2, page 810). The authors are optimistic for the emerging potential of BMDCs, but the reality was, and still is, that the state of the pertinent art has not developed to the extent that enabling a therapeutic use for ameliorating any symptom of Parkinson's disease at the time of instant priority date.

Hence, in view of the state of the art years after instant filing date, it is not appropriate to extrapolate the results of the mouse model to treating PD in humans, and it is highly unpredictable whether the functional improvement observed in a mouse model could extend to a human subject suffering from PD. The success in mice has yet

to be translated into clinical benefit in the pertinent art for treating human Parkinson's disease.

The claims are drawn to treating a neuronal deficiency comprising administering bone marrow-derived cells by vascular administration to an individual having a neuronal deficiency caused by Parkinson's disease, wherein the cells are from *self* or an allogenic origin, wherein at least one symptom of the neuronal deficiency are ameliorated. The claimed invention is highly unlikely to be enabled because how one explains the fact that a PD patient has normal bone marrow cells, yet PD still arises and progresses in the PD patient? To this end, any reasonable skilled would not comprehend how simply transplanting the bone marrow cells of a PD patient back to the patient would treat neuronal deficiency of the PD. Hence, based on a common sense, transplanting autologous bone marrow from a PD patient to treat PD is unlikely to be successful. And one cannot simply extrapolate from a mouse model to predict the same treatment strategy would work in humans.

The claims broadly encompass any vascular delivery of BM-derived cells. The working example of the specification uses tail vein infusion. It is noted although it seems that any number of means can deliver the BM-derived cells to circulation, the results are not always predictable. For example, it is known in the art certain tumor metastatic model may be established only by intravenous delivery but not via artery system. Factors yet unknown may influence the traveling pattern, homing, and engraftment of implanted cells. As taught by *Hows et al*, it is currently unknown and the specification

fails to teach the homing mechanism of the bone marrow cells. Thus, instant disclosure only provides enablement for *intravenous* delivery.

As to the fractionation of bone marrow cells, applicant argues such fractionation is not a requirement of the claimed invention.

In response, instant claims require the use of "bone marrow-**derived** cells", rather than bone marrow cells, and fractionation is a preferred embodiment as indicated in paragraphs 82-83. Since the specification does not clearly define what "derived" encompasses or excludes, fractionation could be reasonably interpreted to be encompassed by the derivation. Accordingly, it appears fractionation is a required component of the claimed invention.

Accordingly, in view of the quantity of experimentation necessary to determine the outcome of bone marrow transplantation in PD patients, and at therapeutic levels, in particular for the treatment of PD, the lack of direction or guidance provided by the specification as well as the absence of working examples with regard to functional aspect of the engrafted cells in the brain, and the breadth of the claims directed to the treatment of Parkinson's Disease with any fraction of bone marrow-derived cells, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(f) he did not himself invent the subject matter sought to be patented.

Claims 1, 4-13; 15-17, 21 stand rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter.

Claims 1, 4-13, 15-17, 21 are directed to an invention not patentably distinct from claims 1-21 of commonly assigned U.S. patent application 10/688,747. Specifically, claims of co-pending application embrace instant claims.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned application, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. **102**(e), **(f)** or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned **at the time the invention** in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. **102(f)** or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

Applicant argued that the present invention precedes in filing date [of] the 10/688,747 patent [application], therefore cannot serve as prior art.

In response, the statute set forth in 35 U.S.C. 102(f) does not require an inquiry into the relative dates of a reference (MPEP 2137). The court has established, although derivation and priority of invention both focus on inventorship, derivation addresses originality (i.e., who invented the subject matter), whereas priority focuses on which party first invented the subject matter. Price v. Symsek, 988 F.2d 1187, 1190, 26 USPQ2d 1031, 1033 (Fed. Cir. 1993). Thus, 35 U.S.C. 102(f) may apply where 35

U.S.C. 102(a) AND 35 U.S.C. 102(e) are not available statutory grounds for rejection.

Accordingly, it is applicant's duty to clarify the record.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 4-13, 15-17, 21, and 36 stand or newly provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-21 of copending Application No. 10/688,747.

Applicant requested that this rejection be held in abeyance until the finding of allowable subject matter.

Until then the rejection stands for reasons of record.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is **571-272-0730**. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of formal matters can be directed to the patent analyst, **William Phillips**, whose telephone number is (571) 272-0548.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is **(866) 217-9197**. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

Q. JANICE LI, M.D.
PRIMARY EXAMINER

Q. Janice Li, M.D.
Primary Examiner
Art Unit 1633

QJL
November 27, 2006